A meta-analysis of individual patient data: significant reduction in non-vertebral fractures with high- versus low-dose ibandronate

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SUMMARY

- In the 3-year BONE study (oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe) in women with postmenopausal osteoporosis, daily oral ibandronate (Boniva®) 2.5mg significantly reduced vertebral fracture risk by 62% vs placebo (p=0.0001).[1]
- Although non-vertebral fracture efficacy was not shown in the overall study population, who were at relatively low risk for such fracture, a significant reduction in non-vertebral fracture risk (69% vs placebo; p=0.012) was seen in a subgroup of patients who were at increased risk for fracture (baseline femoral neck bone mineral density [BMD] T-score <–3).[1]
- Analyses of BMD data show that compared with the 2.5mg daily regimen, licensed doses of ibandronate (monthly oral 150mg and quarterly intravenous [IV] injection 3mg) are superior, predicting that they may also have improved antifracture efficacy.[2]
- These doses provide an annual cumulative exposure (ACE) of ≥10.8mg compared with 5.5mg for the daily oral regimen (2.5mg)
  - ACE is calculated by multiplying the dose of medication by the number of annual doses and an absorption factor (0.6% for oral dosing; 100% for i.v.).
- A meta-analysis of individual patient data was performed to assess the effect of different doses of ibandronate on non-vertebral fractures.
- All randomized, controlled trials of ibandronate were reviewed and two trials were selected for inclusion in the analysis as they were identical in study design
  - different total doses of ibandronate based on ACE were explored.
- A significantly reduced rate of non-vertebral fractures was seen when combined doses (ACE groups 12mg and ≥10.8mg) were compared with ACE 5.5mg
  - in addition, there was a dose-response trend with increasing ACE (7.2–12mg) compared with ACE 5.5mg.
- Overall, treatment effects on non-vertebral fractures were dose dependent. A significant effect on non-vertebral fracture risk reduction was seen when ibandronate doses providing ACE ≥10.8mg were compared with ACEs of 5.5mg and ≤7.2mg.
- These data suggest improved fracture efficacy for ibandronate doses with an ACE >10.8mg, which includes the licensed 150mg once-monthly oral and 3mg quarterly IV injection doses versus oral daily dosing, a regimen with proven fracture efficacy.[1]

INTRODUCTION

- In the BONE study, daily oral ibandronate 2.5mg showed significant antifracture efficacy, with a 3-year vertebral fracture risk reduction of 62% vs placebo (p=0.0001).[1]
- Non-vertebral fracture efficacy was not shown in the overall study population, who were at relatively low risk for such fractures (femoral neck BMD T-score –2.0)
  - however, a reduction in non-vertebral fracture risk of 69% (p=0.012) was shown in patients who were at increased risk for fracture (baseline femoral neck BMD T-score <–3).[1]
- Licensed doses of ibandronate (once-monthly oral 150mg and quarterly IV injection 3mg) have demonstrated substantial BMD gains and marked reductions in bone turnover markers when compared with daily oral ibandronate (2.5mg)[3,4]
  - these doses, administered with extended dosing intervals, deliver an ACE of ≥10.8mg vs an ACE of 5.5mg for the daily regimen and could potentially have significant antifracture efficacy.[2]
- To investigate this hypothesis, a meta-analysis of individual patient data was used to assess the effect of different doses of ibandronate on non-vertebral fractures.

METHODS

Study design and objectives

- The aim of the meta-analysis was to characterize the non-vertebral antifracture efficacy of ibandronate doses used in clinical practice (monthly oral 150mg and quarterly IV injection 3mg)
  - key principles for meta-analyses methodology have been applied. Previously conducted meta-analyses in osteoporosis have used summary data, whereas the current analysis used individual patient data.[5]
- The outcome measure was defined as the hazard ratio (HR) of sustaining a non-vertebral fracture
  - HR is an estimate of relative risk, e.g. a HR of 0.5 equates to a relative risk reduction of 50%
  - non-vertebral fractures were defined as fractures of the clavicle, humerus, wrist, pelvis, hip and leg.
- A systematic review identified eight randomized, controlled ibandronate trials that were reviewed for inclusion in the meta-analysis.
- Two trials were selected: the 2-year MOBILE (Monthly Oral Ibandronate in LadiEs) and DIVA (Dosing IntraVenous Administration) studies were selected for the meta-analysis as they contained appropriate data (i.e. fracture incidence data) for different dose levels of ibandronate, including the licensed monthly oral 150mg and quarterly IV injection 3mg regimens and both studies were of similar study design.
- To account for the different dosing regimens used in each of the studies, dose categories were grouped based on ACE
  - ACE is the total quantity of active medication received by the patient over a 1-year period, allowing for bioavailability
  - calculated as the dose of medication (in mg) x the number of annual doses x an absorption factor (0.6% for oral dosing, 100% for i.v. dosing)
    - oral: 12mg x 12 annual doses x 0.6% = 10.8mg
    - i.v.: 3mg x 4 annual doses x 100% = 12mg.
- The different ACE levels, calculated from the doses of ibandronate administered during the selected trials, were grouped into five categories, based on level of exposure
  - ACE 12mg includes dosing regimens: 3mg every 3 months [q3mo] i.v. and 2mg every 2 months [q2mo] i.v.
  - ACE ≥10mg includes dosing regimens: 3mg q3mo i.v., 2mg q2mo i.v. and 150mg monthly oral
  - ACE ≥7mg includes dosing regimens: 3mg q3mo i.v., 2mg q2mo i.v., 150mg monthly oral, 50+50mg monthly oral and 100mg monthly oral
  - ACE 5.5–7.2mg includes dosing regimens: 50+50mg monthly oral, 100mg monthly oral and 2.5mg daily oral
  - ACE 5.5mg includes dosing regimens: 2.5mg daily oral only.

Statistical considerations

- An exploratory approach comparing different doses based on ACE was employed.
- A one-stage model was used[6] and trial randomization was maintained.
- Non-vertebral fractures at 2 years were assessed by a time-to-event analysis using Kaplan-Meier methodology, with treatment effect (HR) derived from a Cox model.
- The potential effect of covariates recorded at baseline was analyzed and included clinical fracture history, age and BMD (full model then stepwise).

RESULTS

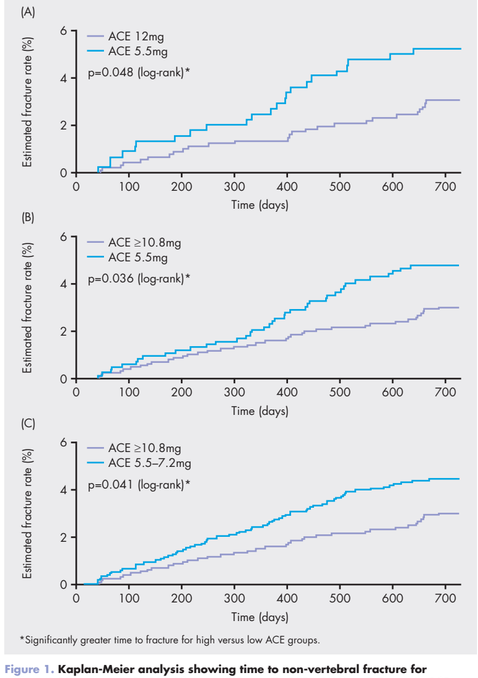
- When dose groups comprising ACE 12mg and ≥10.8mg were compared with ACE 5.5mg, a significantly reduced rate of non-vertebral fractures was seen after 2 years (**Table 1**)
  - there was a dose-response trend with increasing ACE (7.2–12mg) compared with ACE 5.5mg.

Table 1. Risk of non-vertebral fractures with ibandronate by ACE groups.

High ACE	Low ACE	Patients (n)	Adjusted HR (95% CI)	RR (%)	p value*
12mg	5.5mg	1,355	0.569 (0.324, 0.997)	43	**0.0489**
≥10.8mg†	5.5mg	2,137	0.620 (0.395, 0.973)	38	**0.0375**
≥7.2mg	5.5mg	2,921	0.745 (0.504, 1.102)	26	0.1402
≥10.8mg†	5.5–7.2mg	2,921	0.634 (0.427, 0.943)	37	**0.0243**

*Cox-regression analysis for difference between fracture incidence
†Includes marketed ibandronate doses monthly oral 150mg and quarterly IV injection 3mg
RR = risk reduction

- Similar results were seen when ACE ≥10.8mg was compared with ACE ≤7.2mg (HR: 0.634; 95% CI: 0.427, 0.943; p=0.0243).
- Adjustment of HRs for covariates (clinical fracture history, age and BMD) had a minimal effect on results.
- Kaplan-Meier analysis performed for different dose groups showed that time to non-vertebral fracture was significantly extended for ACE groups 12mg and ≥10.8mg compared with ACE 5.5mg and ≤7.2mg
  - ACE 12mg vs ACE 5.5mg, p=0.048 (**Figure 1A**)
  - ACE ≥10.8mg vs ACE 5.5mg, p=0.036 (**Figure 1B**)
  - ACE ≥10.8mg vs ACE 5.5–7.2mg, p=0.041 (**Figure 1C**).



*Significantly greater time to fracture for high versus low ACE groups.

Figure 1. Kaplan-Meier analysis showing time to non-vertebral fracture for different ACE groups: (A) ACE 12mg vs 5.5mg; (B) ACE ≥10.8 vs 5.5mg; (C) ACE ≥10.8mg vs 5.5–7.2mg.

CONCLUSIONS

- This meta-analysis of data from two 2-year, pivotal, phase III studies of ibandronate monthly oral or quarterly IV injection showed that dosing regimens with an ACE ≥10.8mg are associated with significant benefits on fracture risk compared with ACE 5.5–7.2mg in women with postmenopausal osteoporosis after 2 years.
- Kaplan-Meier analysis showed that doses in ACE groups of 12mg or ≥10.8mg resulted in extended time to non-vertebral fracture versus ACE groups of 5.5–7.2mg.
- These data indicate improved non-vertebral fracture efficacy for the licensed and marketed ibandronate monthly oral and quarterly IV injection regimens versus oral daily ibandronate, which has previously demonstrated significant vertebral fracture efficacy versus placebo, and non-vertebral fracture efficacy in a high-risk sub-population.[1]
- This meta-analysis provides strong evidence that the currently available and marketed once-monthly oral and quarterly IV ibandronate doses are efficacious at all fractures sites.
- This is unique evidence that a licensed bisphosphonate significantly reduces non-vertebral fracture risk with the currently available marketed doses at an extended drug-free interval of more than 2 weeks, which is greater than the lifespan of an osteoclast.

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